Melatonin can either stimulate or inhibit cell proliferation, apparently depending on dosage. Blask and Hill (1986) have shown that physiologic levels of melatonin inhibit cancer cell growth, while sub- and super-physiologic levels of melatonin do not. A melatonin-induced proliferation of the erythroid- and myeloid-bone-marrow cell compartments has been observed which apparently extends to all body cells (Di Bella et al., 1979). The growth of lung, stomach, and breast cancers; lymphoma; and bone sarcoma were depressed with melatonin treatment; the survival time of patients was increased and symptoms alleviated (Di Bella et al., 1979). This treatment is potentiated by simultaneously lowering the levels of circulating growth hormone. In vitro, melatonin exhibits oncostatic properties against certain cancer cell lines including carcinomas and breast cancer (Blask and Hill, 1986; Rodin, 1963). Melatonin has also been used in the treatment of leukopenia, in both chronic and acute lymphoblastic leukemia and during antiblastic chemotherapy (DiBella et al., 1979). In contrast, there have been other reports indicating that the pineal gland either has no effect on or stimulates the growth of some tumors (Kachi et al., 1988).

The inconsistent results of animal studies on the pineal gland and its hormones could be due to the dependence of pineal response on the photoperiodic environment (Reiter, 1988). Of particular importance is the timing of the administration of melatonin, which is most effective in pineal-intact animals when given late in the light period (Reiter, 1988).

5.7.2. Extremely Low Frequency Fields

Based on experimental evidence that shows an effect of light and ELF electric and/or magnetic fields on pineal melatonin production, and on the relationship of melatonin to mammary carcinogenesis, Stevens (1987) has proposed a hypothesis that the use of electric power may increase the risk of breast cancer.

Pineal production of the hormone melatonin, which shows a distinct circadian rhythm, is suppressed by light. The circadian rhythm is evident in blood and pineal gland levels of melatonin: low levels in daylight and high levels at night (Tamarkin et al., 1985). Melatonin, in turn, suppresses prolactin production by the pituitary and estrogen production by the ovary (Mhatre et al., 1984).

If circulating levels of melatonin are reduced (by pinealectomy or constant-light exposure), the growth of DMBA-induced mammary tumors in the rat is accelerated (see Section 5.7.1). Stevens (1987) proposes a scheme through which long-term exposure to ELF fields may act as a "functional pinealectomy" and enhance mammary DMBA-induced carcinogenesis in rats (Figure 5-1). The hypothesis is based on the idea that melatonin level affects production of prolactin and estrogen, and that it is the action of these hormones that increases breast cancer risk by increasing stem cell turnover. In addition, Wilson et al. (1988) propose that ELF may also have an effect on steroid hormone-promoted prostate cancers.

Wilson et al. (1981, 1986) demonstrated that melatonin production can be suppressed by a 60-Hz field. Male Sprague-Dawley rats were acclimated to a daily 14-hour light:10-hour dark photoperiod at 21° C and 20% to 40% relative humidity (Wilson et al., 1981). At 56 days of age, 20 animals in electrical contact with the reference ground electrode were exposed to a uniform, vertical 60-Hz field (field strength, 1.7 to 1.9 kV/m) in a parallel-plate exposure system. The animals were exposed 20 hours per day for 30 days. At the end of exposure, animals were killed in groups of 10 (5 exposed, 5 sham-exposed) at four different times during the light/dark cycle (1400 [light], 2200 [dark], 0200 [dark], and 0800 [light] hours). All conditions were the same for : exposed and sham-exposed animals except for the presence or absence of the electric field. Pineal glands were removed and quick-frozen usually within 2

Chronic 60-Hz Electric Field

↓

Pineal Gland: Reduced Melatonin Production

↓

Ovary: Constant Estrogen
Pituitary: Constant Prolactin

↓

Increased Turnover of Breast Epithelial Stem Cells at Risk

↓

Increased DMBA Mammary Carcinogenicity

Figure 5-1. Proposed mechanism by which chronic exposure to a 60-Hz electric field may increase dimethylbenz[a]anthracene (DMBA) -induced mammary carcinogenesis in rats.

SOURCE: Adapted from Stevens, 1987.

minutes of death. Pineal melatonin was assayed by gas chromatography/mass spectrometry using an internal standard and the data were analyzed by analysis of variance.

Exposed rats, killed at 0200 hours, showed a significant ($p<0.05$) reduction in melatonin levels compared with control rats. During the dark phase, there was a significant increase ($p<0.01$) in pineal melatonin of the sham-exposed animals, but no increase in the field-exposed animals ($p<0.20$), based on the internal standard. In a duplicate experiment, the melatonin data followed the same pattern; however, there were large variances in the data, so the two sampling times in the dark period (2200 and 0200 hours) were combined and the light-period sampling times (1400 and 0800 hours) were combined. Melatonin levels for sham-exposed rats differed significantly ($p<0.002$) between light and dark periods; in contrast, no significant differences were seen in melatonin levels of exposed animals between dark and light periods ($p>0.05$).

In a similar study Wilson et al. (1983) reported that exposure to 60 kV/m also suppressed the nocturnal increases in melatonin. The suppression of the normal nocturnal increase for melatonin was consistent with a reduction in serotonin N-acetyl transferase (SNAT) activity (the rate-limiting enzyme in the synthesis of melatonin from serotonin). Further studies, in which rats were exposed for 3 weeks to 60-Hz, 39 kV/m electric fields, demonstrated that the time required for recovery of the melatonin rhythm after cessation of field exposure was less than 3 days, indicating the overall metabolic competence of the pineal is not permanently compromised by electric-field exposure (Wilson et al., 1986).

5.7.3. Modulated Radiofrequency Fields

No data were found.

No Research

RESEARCH NEEDED

5.7.4. Unmodulated Radiofrequency Fields

Elder et al. (1984) reviewed the effects of RF fields on endocrine gland function and concluded that changes reported in hormonal activities and blood chemistry are similar to those observed during increased thermoregulatory activity and heat stress and are generally associated with SARs >1 W/kg. This conclusion is supported by Elder et al. (1987a, b) in an update of the previous report (Elder et al., 1984). The endocrine effects reported by Elder et al. (1984) appeared to have occurred in the presence of colonic temperature elevations of 0.3° C or more.

5.7.5. Summary

In the preceding sections, studies have been presented that demonstrate that exposure for 3 to 4 weeks to a 60-Hz ELF field suppresses the nocturnal production of melatonin in rats, but that the overall metabolic competence of the pineal is not permanently compromised.

Studies in humans have shown increased serum melatonin levels following chemotherapy and decreased urinary levels in some cases of breast and prostate cancer. In addition, animal and in vitro studies have demonstrated that melatonin can inhibit tumor induction with chemical carcinogens, can inhibit the growth of established tumors, and can enhance the cellular immune response. The results of these studies suggest that there is a relationship between cancer and pineal gland function. In other studies, however, melatonin has had either no or stimulatory effects on tumor growth. Some of the inconsistencies in these studies could probably be resolved with improved techniques for dealing with the circadian aspects of pineal gland function.

The suppressive effects of ELF on pineal melatonin production and the general oncostatic properties of melatonin in several endocrine-stimulated tumors provide indirect evidence for the hypothesis that ELF exposure may be a risk factor in the growth of these tumors. Studies that incorporate all three parameters, ELF exposure, melatonin production, and breast cancer induction, are needed for further evaluation of this hypothesis.

In other studies, pineal neurological activity and melatonin synthetic activity were inhibited by static magnetic fields when the orientation of the field was changed by as little as 5 degrees, a change which is only a factor of 10 higher than ambient magnetic residential fields (Welker et al., 1983; Semm et al., 1980). These studies and the role of the retina as the magnetoreceptor (Olcese et al., 1985; Reuss and Olcese, 1986) are discussed in greater detail in Section 5.10.1.

5.8. GROWTH AND DIFFERENTIATION

5.8.1. Extremely Low Frequency Fields

Several studies have demonstrated a growth-enhancing effect of ELF exposures on both normal and neoplastic cells in vitro. The stimulation of the growth of neoplastic cells is of particular concern in the therapeutic treatment of bone fractures with ELF fields in cases where a neoplastic lesion may be present. Because osteogenesis is thought to occur as a result of